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Interruption of visually perceived forward motion in depth evokes a cortical activation shift from spatial to intentional motor regions

A. van der Hoorn^{a,b}, M. Beudel^{a,b}, B.M. de Jong^{a,b,*}

^a Department of Neurology and ^b Neuroimaging Center University of Groningen, Groningen,
The Netherlands

* Corresponding Author

ABSTRACT

Forward locomotion generates a radially expanding flow of visual motion which supports goal-directed walking. In stationary mode, wide-field visual presentation of optic flow stimuli evokes the illusion of forward self-motion. These effects illustrate an intimate relation between visual and motor processing. In the present fMRI study, we applied optic flow to identify distinct interfaces between circuitries implicated in vision and movement. The dorsal premotor cortex (PMd) was expected to contribute to wide-field forward motion flow (FFw), reflecting a pathway for externally triggered motor control. Medial prefrontal activation was expected to follow interrupted optic flow urging internally generated action. Data of 15 healthy subjects were analyzed with Statistical Parametric Mapping and confirmed this hypothesis. Right PMd activation was seen in FFw, together with activations of posterior parietal cortex, ventral V5, and the right fusiform gyrus. Conjunction analysis of the transition from wide to narrow forward flow and reversed wide-field flow revealed selective dorsal medial prefrontal activation. These findings point at equivalent visuomotor transformations in locomotion and goal-directed hand movement, in which parietal–premotor circuitry is crucially implicated. Possible implications of an activation shift from spatial to intentional motor regions for understanding freezing of gait in Parkinson's disease are discussed: impaired medial prefrontal function in Parkinson's disease may reflect an insufficient internal motor drive when visual support from optic flow is reduced at the entrance of a narrow corridor.

RESEARCH HIGHLIGHTS

- Radial expanding optic flow generates the illusion of forward locomotion.
- Forward optic flow activates motor circuitry via the lateral premotor cortex.
- Medial prefrontal activation occurs at narrowing radial expanding optic flow.

INTROCUCTION

Forward locomotion generates a characteristic streaming motion of environmental features through the visual field. This 'optic flow' implies a radial expansion from the central point on the horizon ahead, provided that the observer does not fixate a specific object (Gibson, 1954; Wurtz et al., 1993). Distant objects are located near the center of the visual field and move slowly from it, while nearby objects are in the peripheral field and move further in eccentric direction with increasing speed. In stationary condition, a similar sensation of forward self-motion can be evoked by presenting a pattern of expanding radial optic flow in the lower part of the visual field (Kovács et al., 2008). This visual effect is in line with the finding that humans make use of optic flow to walk to a goal (Warren et al, 2001). The latter suggests visuomotor coordination equivalent to the support of visual information to accomplish adequate reaching movements (Johnson et al., 1996; Sakata et al., 1997).

In Parkinson's disease (PD), which is predominantly characterised by motor symptoms such as rigidity and bradykinesia, support of sensory cues on walking is illustrated by gait improvement that has been demonstrated by the presentation of parallel traverse lines on the walking surface (Azulay et al., 1999; Suteerawattananon et al., 2004). Suppression of this gait improvement by stroboscopic light further demonstrated that perceived motion of the stripes, induced by the patient's walking, was an essential aspect of gait support and favoured the involvement of visuomotor circuitry responsive to rapidly moving targets (Azulay et al., 1999). In contrast to the supportive effects of sensory cues, incompatible stimuli may obstruct intended movements in PD and may even result in deviant movement patterns aligned to these external cues (Freeman et al., 1993; De Jong et al., 1999). With regard to gait, such motor blocking occurs at the transition to narrow spaces (Giladi et al., 1992; Okuma, 2006). Given the impact of optic flow on gait, both in normal conditions and in PD, we employed

functional magnetic resonance imaging (fMRI) to gain further insight in the interconnection between pathways involved in processing optic flow and circuitry implicated in motor control.

Functional imaging of the human brain has demonstrated that visual motion processing strongly involved activation of extrastriate visual area V5 (Watson et al., 1993; Tootell et al., 1995), while the specific perception of forward motion in depth was related with activations distributed over extrastriate visual regions ventral to V5 (the fusiform gyrus), dorsal V3, and the dorsolateral precuneus of the superior parietal lobe (De Jong et al., 1994; Morrone et al., 2000; Kovács et al., 2008). Particularly, the parietal involvement was proposed to reflect the ability to play a central role in visuomotor coordination, i.e., control of locomotion, integrated with temporal cortex processing associated with the perception of the environmental scene. Widely described functional interconnection between posterosuperior parietal areas and dorsolateral premotor regions in visuomotor coordination underscores that external stimuli indeed efficiently influence motor control (Wise et al., 1997; Clavagnier et al., 2007). Prefrontal cortical regions, on the other hand, may exert an inhibitory effect on such external triggers, complementing the internal generation of movements (De Jong and Paans, 2007; Koechlin and Hyafil, 2007). With regard to internal movement generation, particularly medial frontal regions such as (pre-) supplementary motor area (SMA) and medial prefrontal cortex have been reported to play a prominent role (Lau et al., 2004; Rushworth, 2008; Brass and Haggard, 2008). These frontal regions are major output targets of the basal ganglia, reached via the thalamus (Middleton and Strick, 2000). Dysfunction of such projections in PD leads to a disturbed balance between external and internal impacts on the cerebral organization of movement, with increased vulnerability to external cues (Praamstra and Plat, 2001; Hallett, 2008) that may either enhance or obstruct intended movements.

In the present study, on healthy subjects, we aimed to explore how visual stimulation might influence cerebral circuitry implicated in gait control. To that end, we presented wide-field radially expanding optic flow, mimicking the perception of forward motion in depth, followed by a transition to a narrow flow field. We hypothesized to find activations evoked by wide-field forward flow in the parietal and dorsal premotor cortex (PMd), while such activations were expected to stop at the transition to the narrow flow field. At this transition, medial prefrontal activation was expected to occur, reflecting a functional shift between circuitries implicated in respectively externally enhanced and internally generated motor control. Given the fact that motor-related cortical circuitry maintains a level of intrinsic activation in resting state without a specific motor task (Xiong et al., 1999), we assumed it plausible that specific visual stimulus conditions might indeed interact with such functional circuitry. To deal with the bias related to the size of the visual field, a condition with reversed wide-field flow was included. Compared to forward flow, less biological significance with regard to locomotion has been attributed to such reversed flow (Ptito et al., 2001; Wunderlich et al., 2002).

METHODS

Fifteen healthy right-handed subjects, mean age 23 yr ($SD \pm 4.2$), 8 females, successfully participated in this study. None of the subjects had neurological, ophthalmologic, or upper extremity disorders. They signed an informed consent to a protocol approved by the Medical Ethics Committee of the University Medical Center Groningen. Procedures and task instructions were explained minimally 1 week before scanning as well as immediately before the experiment.

Task design

During scanning, subjects watched the stimuli on a screen of 44 by 34 cm², comprising 25.5° by 32.7° of the visual field. This screen was visible through a mirror placed 11 cm in front of the

face and 64 cm from the display screen. A beamer with a monitor refresh rate of 30 Hz and a resolution of 1024×768 pixels (Barco, Belgium) projected the computer-generated stimuli on the screen. The experimental conditions were presented in a pseudo-randomized order using the "Presentation" program (Neurobehavioral Systems, Inc. Albany, CA, USA). All conditions consisted of white dots in the lower half of the monitor screen, on a black background (Fig. 5A). At the middle of the virtual horizon, a short horizontal line was placed for gaze fixation. A few observations outside the MR scanner confirmed that subjects easily maintained fixation at this central marker, from which one might infer similar levels of attention. Moving stimuli consisted of 25 frames in a second. The mean density of the dots was approximately 340 over the lower half of the display, while each dot was moving with a linear acceleration from the centre to the periphery in 2 s. The mean speed of each dot was 4.9° in the first second and 7.9° in the last second, reaching a maximum of 26° per second just before the dot leaves the screen.

In condition 1 ('forward wide flow') (FFw), dots moved radial from the centre of the virtual horizon with increasing speed in the lower part of the monitor. During this acceleration, the dots proportionally enlarged. In condition 2 ('reversed wide flow') (RFw), direction of the moving dots was reversed. Now, dots moved from the periphery of the lower part of the monitor with decreasing speed to the centre of the virtual horizon. The gradual transitions from a wide to a narrow field of stimuli (Fig. 5B) was established by surfaces (in dark grey tone) that expanded in 1 s from the horizon in both upward and downward directions, leaving a central vertical of 4% (1.3°) in the visual field. This transition occurred in both forward wide flow (condition 3) (FFt) and in reversed wide flow (condition 4) (RFt). Although the occluding surfaces expanded from the horizon in both upward and downward directions, the transition was particularly perceived as a loss of the presented dots in the lower visual field. The present design thus provided the illusion of entrance in a narrow corridor of which the specific

characteristics remained undefined (condition 3, FFt). The absence of distinct objects in the approaching 'scene' is a difference with the recent study of Wolbers et al. (2008). In conditions 5 and 6, the narrow optic flow field was presented in respectively 'forward' and 'reversed' directions. Condition 7 served as control condition in which the dots were presented in stationary mode (Cstat).

Subjects were in the scanner for about 40 min. The stimuli were presented in a block-design with six different blocks, equally divided over two runs. Each block contained 12 trials consisting of a fixed sequence of conditions, i.e., stationary control, wide field flow, transition, and narrow flow. Six of such trials had flow in forward mode while it was in reversed mode in the other six trials. In this way, each of the conditions 1–6 was repeated 36 times. The order of trials regarding forward or reversed flow was randomized and balanced. The transition from the wide to narrow field of flow lasted 1 s (and was demarcated as a distinct condition). The onset of this transition varied in time to prevent stimulus anticipation. As a consequence, a wide flow field lasted either 6, 7, 8, 10, 11, or 12 s, complemented by a successive narrow field of respectively 12 to 6 s. As the initial stationary control condition lasted 6 s, each trial lasted 25 s (Fig. 6). Wide field stimuli were always presented before the narrow field. This bias in the sequence of conditions was an intrinsic element of the design because, regarding transitions, our research question only concerned cerebral activations related to the transition from wide to narrow forward flow.

MRI characteristics

Data acquisition was performed using a 3-T Philips MR system (Philips Medical Systems, Best, The Netherlands) with a standard 6-channel SENSE head coil. Functional images were acquired with a gradient-echo T2* blood oxygen level dependent (BOLD) contrast technique using the following scanning parameters: TR = 2000 ms, TE = 28 ms, 39 slices, isotropic voxels $3.5 \times 3.5 \times$

3.5 mm³, 5° axial orientation. Two runs of 460 volumes each were obtained. A T1-weighted 3D anatomical scan was acquired to obtain high-resolution anatomical information.

Analysis of fMRI data

Image processing and statistical analysis (voxel-based, whole brain) were conducted with Statistical Parameter Mapping (Friston et al., 1995), version 5 (2005, Wellcome Department of Cognitive Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>). All volumes obtained were used for data analysis. Preprocessing with SPM included realignment, coregistration, and spatial normalization (template of Montreal Neurological Institute, MNI). After this, a Gaussian filter of 8 mm full-width at half-maximum was applied to smooth the data spatially. Cerebral activations were rendered either onto T1 brain slices or on the surface of a standard MNI brain.

For the statistical analysis of regional differences in cerebral activation, all conditions were modelled in a block design at subject level. To identify distributions of activations related to characteristics of visual motion processing in conditions 1–4, each of these conditions was implicitly contrasted to the stationary condition 7 at subject level. This allowed the confirmation of expected visual cortex activations, and further provided an initial assessment of the responses in the PMd and medial prefrontal cortex. Thereafter, each contrast was separately analyzed at group level using one-sample t tests. Differences between conditions were analyzed (at second level) with a one-way ANOVA for repeated measures (random effect analysis). The contrasts of conditions 1–4 were used in the ANOVA using direction and transition as factors, both with the possibilities forward and reversed. Conditions were assumed to be dependent, equally variant with regard to flow direction and unequal for visual field width, whereas subjects were assumed to be independent and equally variant. Contrasts between the experimental conditions were primarily made to compare FFw with RFw

(condition 1 > 2). In addition to the comparison of FFt with stationary control (condition 3 > 7), from which we expected to find medial prefrontal activation associated with internally driven motor control following reduced visual support, we contrasted both FFt and RFw (conditions 3 and 2) with FFw (condition 1). To identify overlap in the resulting activation increases, we performed a conjunction analysis (inclusive masking) of conditions 3 > 1 and 2 > 1. This analysis thus provided the opportunity to optimally assess activations related internal motor generation, with a balanced presentation of stimuli within the visual field. The resulting set of voxel values for the indicated contrasts constituted the associated SPM of the t-statistics (SPM < T>) and were thresholded at initial voxel response height $P < 0.001$ with extent threshold $k = 8$ voxels. Resulting clusters of increased activation were considered statistically significant at cluster-level $P < 0.05$, corrected for the entire brain volume.

As we had specific hypotheses for effects in the dorsolateral premotor cortex and the medial prefrontal cortex (including the pre-SMA), the data were additionally explored at a relaxed threshold of $P < 0.05$ (voxel-level, uncorrected). In addition, profiles of the BOLD response in the resulting voxel clusters at these two locations were assessed by region of interest (ROI) analyses using MarsBar in the SPM toolbox. In this, condition-specific values for FFw, FFt, RFw, and RFt were expressed as a percentage of the overall error term and were corrected to a mean of 0. Differences between these four conditions regarding BOLD profiles in the concerning clusters were analyzed by using SPSS version 16.0. Homogeneity of variance was tested with Levene's test for equality of variance. The variance was equal between (i) FFw and RFw and (ii) FFt and RFt but differed between these two pairs. As it has been shown that the F-test is still quite robust by inequality of variance, an ANOVA could be used. Correction for multiple comparisons implied that the threshold for statistical significance was set at $P < 0.0125$ for the post-hoc tests.

Assessment of the illusion of self-motion

All subjects reported the illusion of forward self-motion during FFw in the MR scanner. This was not formally tested. A few weeks after the fMRI study, we obtained quantitative assessments from 10 of 15 subjects who participated in the study. The criterion for this subject selection was based on the travel distance to Groningen. Subjects were instructed to rate the strength of the illusion of self-motion on a scale that ranged from 0 (no motion illusion) to 10 (very strong illusion). Stimuli were presented on a computer monitor (VAIO laptop, Sony, Japan) in the same visual field of view as during fMRI. The following stimulus conditions were presented five times each: Cstat, FFw, RFw, and a narrow field of forward motion flow. They were ordered in five blocks, of which each block contained the four conditions in random order. Paired t-tests were used for the statistical analysis of differences in ratings that were given to the four conditions. As a total of six paired t-tests were performed, including Bonferroni correction, statistical significance was set at $P < 0.008$.

RESULTS

The illusion of self-motion

The control static stimulus display (Cstat) did not evoke any sensation of self-motion and was rated 0 ± 0.1 (mean \pm SD). The scores for wide forward flow (FFw), wide reversed flow (RFw), and narrow-field forward flow were $6.8 (\pm 2.4)$, $6.3 (\pm 2.7)$ and $3.0 (\pm 1.9)$, respectively. Ratings for these visual motion conditions were significantly different from the score attributed to Cstat ($P < 0.001$). The illusion of self-motion evoked by each of the two wide-field optic flow conditions was significantly stronger than the sensation evoked by the narrow flow field ($P < 0.001$). No significant difference was found between ratings for this illusion in FFw and RFw. One might consider that although FFw mimics the most natural circumstance of perceived

forward self-motion, reversed flow is a visual experience which became particularly familiar in modern life, e.g., during travelling in a train seated backwards.

Forward wide flow

Cerebral activations related to the perception of forward self-motion were identified by contrasting FFw to Cstat (condition 1 > 7). Significant increases were distributed around the posterior part of calcarine sulcus, including the fovea representation in the primary visual cortex (V1) and over the lateral extrastriate visual cortex (with putative area V3) extending into the visual motion area V5 (Fig. 1). Particularly, on the right side, the cluster that included V5 spread ventrally. In dorsal direction, significant increases were bilaterally found at the junction of the occipital and parietal cortex around the posterior part of the intraparietal sulcus (pIPS) and in the superior parietal cortex at more anterolateral locations (Fig. 1). The coordinates of these clusters are specified in Table 1.

When RFw was contrasted to Cstat (condition 2 > 7), no significant activations were seen in the parietal cortex (Fig. 1B and Table 1). The finding that parietal activation appeared to occur specifically in FFw was confirmed by the direct contrast of FFw to RFw (condition 1 > 2), although the circumscribed activations in the right superior parietal cortex (x 22, y -58, z 60) and right inferior parietal cortex (x 34, y -34, z 52) remained below formal statistical significance ($P < 0.001$, voxel-level, uncorrected). Significant increases of activation related to FFw, when compared to RFw, were particularly seen at the ventral parts of V5, bilaterally, and the right fusiform gyrus ($P < 0.05$, volume-corrected) (Fig. 1 and Table 1).

The preceding visual and parietal cortex activations mainly concerned replications of previously described findings. In the next part of the results section, the condition-related

effects in motor-associated regions are treated, and activations related to the shift from wide to narrow forward flow are presented. These findings concern the primary scope of this study. Since we had a specific hypothesis that predicted increased activation in the PMd during FFw, possible effects in this region were also assessed at relaxed threshold. At $P < 0.05$ (voxel-level, uncorrected), increased activation was seen at the junction of the lateral aspect of the right superior frontal gyrus and the precentral gyrus, functionally classified as part of the PMd, Brodmann's area BA 6 (x 28, y -6, z 52) (Fig. 2A). No medial frontal activations were seen at this relaxed threshold, while a pattern of distinct parietal activations was seen along the (medial) wall of the intraparietal sulcus, bilaterally (Fig. 2A). The 10 subjects who rated the perceived illusion of forward self-motion in FFw experienced this illusion with scores that ranged between 3 and 9 (scale 0–10). Pearson's correlation between the strength of illusion and the effect in the PMd was 0.31 ($P = 0.38$, two-tailed).

Transition from forward wide to narrow flow

The pattern of significant cerebral activations related to the transition from the wide to the narrow field of forward optic flow (FFt), when compared to Cstat (condition 3 > 7), included the ventral part of V5 and lateral occipital cortex. The FFw-related activations in foveal V1 and the parietal cortex were no longer seen (Table 2). At a relaxed threshold of $P < 0.05$ (voxel-level, uncorrected), activation was seen in the dorsal medial prefrontal cortex with focus of maximum in the left hemisphere (x -8, y 26, z 48) (Fig. 2B). At this relaxed threshold, PMd had disappeared, which was also the case for the well-delineated superior parietal pattern. Increased activation of V1 was not seen either.

Medial prefrontal activation was hypothesized to occur in response to reduced stimulation of circuitry providing external support for locomotion. It would thus reflect an increased demand on circuitry implicated in organizing the internal generation of motor actions. Next to the

comparison of FFt with Cstat, we contrasted FFt to FFw (condition 3 > 1) which provided further support for medial prefrontal activation during the interruption of perceived forward self-motion (Table 2). This contrast also revealed a bilateral signal increase in the temporal horn of the lateral ventricles, reaching statistical significance on the left side, which might possibly be related to a venous drainage effect following FFw. Alternatively, we considered head motion due to postural adjustment at FFt as a possible cause for artificial signal increases. However, movement parameters that were assessed at single-subject level did not provide support for such explanation. Conjunction analysis of this comparison and the comparison of RFw with FFw (RFw vs. FFw, inclusive masked by FFt vs. FFw) raised statistical significance of specifically the medial prefrontal activation (Fig. 3 and Table 2). This cluster on the medial aspect of the superior frontal gyrus spread between 18 and 38 mm anterior to vertical traversing the anterior commissure (VCA), which implies that it included the rostral segment of the pre-SMA (BA 6) and the prefrontal cortex adjacent to it (BA 8, 9) (Picard and Strick, 1996). The relative effects across conditions FFw, FFt, RFw, and RFt were plotted for the clusters in the right PMd and medial prefrontal cortex (Fig. 4).

The conjunction analysis of FFt vs. FFw and RFw vs. FFw provided an argument against the possible confound that the medial prefrontal activation might be due to a difference in stimulus field width between FFt and FFw. Other possible confounds intrinsically linked to the transition from wide to narrow visual flow fields might concern (i) the presence of less stimulus adaptation, contrast- and signal-to-noise ratio's in FFt compared to FFw and (ii) a nonspecific attention effect associated with the stimulus change. Activation of the medial prefrontal cortex, however, was not explained by these alternative suggestions because it remained present by contrasting both [FFt–FFw] to [RFt–RFw] (Fig. 2D) and FFt to RFt (Fig. 2E), while it was not seen in the initial 2-s frame of the FFw condition following static control (Fig. 2C).

DISCUSSION

The present study was designed to test the hypothesis that visual stimulation by wide-field forward flow (FFw) facilitates activation of cerebral circuitry implicated in externally driven motor control, while the transition to a narrow flow field (FFt) interrupts such facilitation and induces a shift to neuronal circuitry known to support internally driven motor control. Right parietal–premotor activations evoked by FFw provided logical arguments for a potential functional interface between visuospatial motion processing and spatial motor preparation (Wise et al., 1997). The common medial prefrontal activation related to FFt and reversed wide-field flow (RFw) is consistent with this concept and may thus imply that the loss of external support from FFw was complemented by an increased demand on circuitry implicated in the internal generation of motor action (Rushworth, 2008; Brass and Haggard, 2008). Although the present results do not ultimately prove the hypothesized manipulation of motor circuitry, the obtained data provide a clear starting point for future studies to explore this issue.

Wide-field forward optic flow (FFw)

The applied visual motion conditions were contrasted to a control condition in which a fixed image was displayed. As expected, robust increase of activation in the visual motion area V5 (Watson et al., 1993) occurred in all motion conditions. The present paradigm was not primarily designed to discriminate between optic flow and simpler visual motion stimuli such as incoherent motion or parallel translation. On the other hand, the activations in the ventral segment of V5, the right fusiform gyrus, and the dorsal occipitoparietal junction that were particularly seen in FFw and not (or less) in the other motion conditions underscored a distinct relation between these regions and the illusion of forward motion in depth, indeed mimicking the visual feedback arising from natural (forward) locomotion. The specific contributions of

ventral V5 and the adjacent fusiform gyrus to processing optic flow is consistent with previous studies that have addressed the representation of expanding optic flow, as compared to either incoherent motion (De Jong et al., 1994) or parallel translation (Morrone et al., 2000). The increase of activations in such early visual processing areas during FFw, particularly in comparison with RFw, has been proposed to reflect the biological significance of forward motion in depth (Wunderlich et al., 2002). The fact that the flow patterns in FFw and RFw had a similar level of motion coherence indicates that the enhanced activations evoked by FFw, compared to RFw are indeed not explained by only processing three-dimensional structure-from-motion (Braddick et al., 2000; Kourtzi et al., 2008).

Along the posterior segments of the IPS, including the precuneus of the superior parietal lobe, significant activation was evoked by FFw (expanding optic flow) and not by RFw (contracting flow). This difference is consistent with previous studies that showed stronger responses to expanding flow stimuli at this location compared to the responses evoked by incoherent motion (De Jong et al., 1994), parallel translation (Konen and Kastner, 2008), and contracting optic flow (Ptito et al., 2001), respectively. We speculate that this stronger parietal activation in FFw is related to a higher biological significance of forward, compared to backward, locomotion in human. Moreover, the additional anterodorsal parietal activation for which Ptito et al. (2001) described right-sided dominance coincided with the dorsal extension of IPS activation related to FFw in our study. The pattern of activations comprised dorsal and ventral visual processing streams (Goodale and Milner, 1992), which points at circuitry optimally equipped for the integration of visuomotor coordinate transformations and environmental feature identification, as naturally occurs in guiding forward locomotion (de Jong et al., 1994; Andersen et al., 1997; Snyder et al., 1997; De Jong et al., 2001; Aguirre and D'Esposito, 1999; Epstein, 2008; Wolbers et al., 2008).

Although the FFw-related activation in the right PMd did not reach statistical significance after correction for effects in the entire brain volume, the uncorrected result was inferred to reflect a physiological response and not statistical noise. We have three arguments to support this conclusion: (i) the effect was seen in a distinct predefined location; (ii) no other frontal activations were seen in the assessed planes, which supported specificity of the PMd response; and (iii) the right hemisphere location of the PMd activation logically corresponded with the dominance of the right parietal activation during FFw, thus reflecting the expected parietal–premotor coherence (Wise et al., 1997; De Jong et al., 1999).

Spatial processing in the PMd concerns both perceptual and motor functions enabling adequate motor preparation (Johnson et al., 1996; Shen and Alexander, 1997; Bremmer et al., 2001; Pesaran et al., 2006; Beudel et al., 2009). In a recent fMRI study on virtual forward locomotion, the applied visual stimulus design included the incidental (distant) appearance of geometric objects within the expanding flow of dots (Wolbers et al., 2008). Object locations in preceding stationary trials served as a memorized reference enabling subjects to indicate distinct locations in the dynamic trials. Activation profiles in the precuneus and PMd provided arguments for Wolbers and coworkers to propose that the brain uses optic flow for locomotion, in such a way that the precuneus is particularly implicated in successive constructions of updated visuospatial representations while the PMd plays a key role in the context-dependent planning of motor actions. Their specific findings provide strong support for our concept that the parietal and right PMd activations evoked by FFw in the present study indeed point at a distinct neuronal pathway along which visual stimuli may modulate the cerebral organization of motor actions implicated in gait.

We acknowledge that, in our study, the observed effect in the right PMd was not robust. To evoke stronger responses in visuospatial and associated motor regions, further enlargement of

the visual flow field might be considered to achieve a stronger visual resemblance of real self-motion. It is interesting to notice, in this respect, that visual area V6, which has direct connections with the PMd in macaque (e.g., Shipp et al., 1998), has only recently been defined as a distinct visual area in human by using extremely wide-field stimulus presentation (Pitzalis et al., 2006), while involvement of this cortical region in visuomotor functions has previously been a reason to label it the 'human V6 complex' (De Jong et al., 2001). This effect of visual field-width further supports the idea that manipulating the illusion of forward self-motion by distinct changes in radial optic flow is a promising way to study visual modulation of gait control and the underlying functional architecture in the brain.

Aside from visual stimuli, the real perception of self-motion is also derived from other sensory signals such as vestibular, auditory, and tactile information (Britten, 2008). Kleinschmidt et al. (2002) obtained fMRI data on this complex issue by using a rotating windmill pattern that did not change but induced either illusory self-motion (circularvection) or the perception a rotating pattern. The illusion of circularvection, compared to perceived object rotation, was related with increased activation in only the cerebellar nodulus together with general visual and vestibular cortex decreases, which was consistent with vestibular-visual interactions naturally implicated in real self-motion. Unchanged activation levels in both a visual V5 satellite and at the medial parieto-occipital junction were suggested to reflect the ability to maintain a continuous reconstruction of self-motion. This was further motivated by the transient activation increases in the latter during perceptual switches between self-motion and objection motion. These findings may fit our data assuming that the parieto-occipital junction and ventral V5 represent important nodes in an extended visual motion network that efficiently interacts with multiple sensory modalities as well as with (pre)motor regions, which makes it optimally equipped to support locomotion in dynamic circumstances.

Medial prefrontal activation and loss of external motor support

The parietal and PMd activations in our study disappeared during the transition from wide to narrow forward flow (condition FFt) as well in RFw (radially contracting flow). In RFw, the center of maximum within the cluster of V5 activation was dorsal to that in both FFw and FFt. In the preceding paragraphs, we argued that activation of the particular ventral V5 segment in FFw, which occurred together with occipital–parietal activations, supported that the FFw-evoked illusion mimicked the most natural condition of perceived forward self-motion. Persistence of this ventral V5 activation in FFt might thus be related to the fact that subjects still perceived a sense of forward self-motion during narrow forward flow, although less strong than in the wide-field flow condition. The lasting activation of ventral V5 might imply that feature assessment of the virtually approaching dot flow continued with similar intensity, while processing of spatial characteristics and possible visuomotor consequences degraded (De Jong et al., 1994; Tootell et al., 2003; Wolbers et al., 2008).

Complementary to the disappearance of the parietal and right PMd activations, an increase of dorsal medial prefrontal activation was seen during FFt and RFw. Although this medial prefrontal effect was not strong, it was significantly larger in FFt compared to preceding FFw. This effect was consistent with our hypothesis of activated circuitry implicated in internally driven motor control, induced by the loss of external support from optic flow. The involvement of particularly this medial prefrontal activation was further motivated by its selective presence in the subsequent conjunction analysis of FFt and RFw, both compared to FFw (inclusive masking). As this conjunction included wide as well as narrow fields of view, the medial prefrontal effect was not due to change in width of the visual field. The balance in visual field width was a major reason to include RFw in the study, while a reduced biological significance of RFw compared to FFw (Wunderlich et al., 2002) was considered to imply that locomotion with a contracting visual flow field relies stronger on internally driven motor control. The

lateral to medial cortical shift in the present study is consistent with the change from parietal to pre-SMA activation that has recently been described to occur during the intermittent occlusion of feedback in visuomotor control of the upper limb (Ogawa et al., 2006).

Before we further elaborate our conceptual view on the medial prefrontal activation, some remarks need to be made with regard to possible confounds that might alternatively explain this activation. As argued in the preceding paragraph, a difference in width between stimulus fields, which was an intrinsic element of the design, did not account for medial prefrontal activation in FFt. This is also supported by the fact that this activation remained present after contrasting [FFt–FFw] to [RFt–RFw] as well as by comparing FFt to RFt. The latter additionally provided arguments against nonspecific medial prefrontal involvement caused by (i) the difference in stimulus duration between FFt and FFw or (ii) a general effect of shifting between stimulus patterns. Indeed, such shift may induce a change in attention, although easily maintained fixation to the central marker did not indicate an imbalance between conditions in this respect. The medial prefrontal activation thus appeared particularly related to FFt, the condition that mimicked the natural circumstance of approaching a narrow corridor. To which extent a shift between connections to putative motor circuitries might be equivalent to a shift in ‘motor attention’ (Rushworth et al., 2003) remains speculation.

With regard to different motor circuitries, early observations have discriminated selective contributions of the lateral PMd and medial SMA to respectively externally and internally driven movements (Godschalk et al., 1985; Mushiake et al., 1991; Halsband et al., 1993; Passingham, 1993). This general concept has been adapted and refined since. The ordering of specialized regions within the medial prefrontal cortex specified a gradual transformation from intention into action (Rushworth, 2008; Brass and Haggard, 2008). In this, the anterior cingulate cortex plays a role in dealing with stimulus conflicts when they do not unequivocally

code for a specific action (Botvinick et al., 2004; Beudel and De Jong, 2009), while the pre-SMA contributes to the final action selection by inhibition and facilitation of the most appropriate motor repertoires in circumstances of conflicting environmental information (Lau et al., 2006). Moreover, the pre-SMA plays a dominant role in the initiation of movements in the absence of external cues (Lau et al., 2004). The medial prefrontal cortex anterior to the pre-SMA seems particularly implicated in motor selection by inhibition of potentially competing motor acts irrespective of environmental circumstances (De Jong and Paans, 2007; Brass and Haggard, 2007), which is consistent with its proposed role in self-referential mental activity (Gusnard et al., 2001). These previous studies thus support our conclusion that activation of the medial prefrontal cortex in the present study, which partly included the pre-SMA, may reflect an interface between visual processing and circuitry facilitating the internal generation of locomotion when external visual support is interrupted.

In PD, deficit in self-initiated movements has been related to underactivation of the SMA (Jahanshahi et al., 1995). Deprived input from the basal ganglia and thalamus to the medial prefrontal cortex, but also to the lateral premotor cortex, has been shown to cause reduced cortical activity in resting state (DeLong, 1990; Eidelberg et al., 1994), although structural deficit of the medial prefrontal cortex has also been reported (MacDonald and Halliday, 2002). One of the effects of reduced basal ganglia–thalamic input to the lateral premotor cortex is the enhanced influence of external stimuli mediated by the parietal cortex (Samuel et al., 1997; Praamstra and Plat, 2001). This implies that external triggers are difficult to suppress and may result in distracted motor action, while the interruption of supporting stimuli may block ongoing movement patterns. The shift from parietal–PMd activations to medial prefrontal activation that we found in healthy subjects during the transition from wide to narrow forward optic flow may thus help to explain why in PD, a condition with insufficient medial prefrontal cortex function, the internal generation of motor action fails in the circumstance of

interrupted external support from wide-field optic flow. This may indeed result in freezing of gait (Hallett, 2008). Although entrance of a narrow corridor may still evoke a visual flow containing, e.g., characteristics of the corridor's walls, such features remain longer represented in the central parts of the visual field, without an equable shift to the peripheral field. As a consequence, coherence of the visual flow pattern is interrupted in such a way that the sensation of spatial depth is reduced.

In the present experiment, we made use of a visual stimulus paradigm without motor actions. We acknowledge that the activation of cortical regions known to contribute to movement preparation does not prove covert motor involvement in the present task. Our explanation that a change in sensory stimulation modulates activity in motor circuitry, with a shift in dominance from the representation of externally to internally driven motor actions has therefore a tentative character indeed. On the other hand, motor-related cortical circuitry has been demonstrated to maintain a level of intrinsic activation in resting state without a specific motor task. With covariance analysis of fMRI data in resting state, Xiong et al. (1999) demonstrated that spontaneous activations in the motor cortex were related with a distribution of activations in other regions that constituted a functionally interconnected motor network. Such ongoing intrinsic activity in a distinct brain system, without specific task performance, may even be a general rule of cerebral functioning (Raichle and Gusnard, 2005). Raichle and Gusnard (2005) suggested that this ongoing activity provides a condition allowing new sensory information to efficiently modulate the operations of such a functional system. In this respect, visual stimuli might modulate operations of the motor system, aimed to facilitate distinct goal-directed motor preparation, without the necessity of an overt motor response. Future studies, however, need to test the behavioral effects of optic flow modulation on gait control, particularly in patients with PD. In this respect, the experimental paradigm applied in the present study seems to be a promising tool for behavioral and fMRI studies in PD patients.

CONCLUSION

The visual presentation of radially expanding optic flow, which evoked the illusion of forward self motion, activated a putative functional interface with motor-related circuitry distributed over posterior regions of the superior parietal cortex and right PMd. Interruption of such wide-field flow mimicked the loss of external support for locomotion, which may subsequently challenge the medial prefrontal cortex to facilitate internally generated motor action. These results suggest that the cerebral organization underlying visuomotor transformations in locomotion resembles circuitry involved in goal-directed movement of the upper limb.

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Table 1. Cerebral Activations related to the Direction of Radial Optic Flow.

Brain Region (BA)	Left				Right			
	x, y, z	Z-score	Extent	Pcorr.	x, y, z	Z-score	Extent	Pcorr.
<i>Forward Wide Flow vs. Stationary Control</i>								
Foveal V1V2 (17/18)	-26,-102,6	5.46	6155	0.000	28,-96,8	5.42	sc	sc
Lateral occipital (19)	-42,-80,-6	5.33	sc	sc	42,-84,8	5.45	sc	sc
V5 complex (19/37)	-44,-78,-2	5.55	sc	sc	50,-70,-6	5.31	sc	sc
Posterior IPS (19)	-18,-86,44	4.42	sc	sc	26,-74,30	4.35	255	0.000
Superior parietal (7)	-22,-46,48	3.88	117	0.037	30,-52,56	4.39	290	0.000
	-20,-64,62	3.46	38	0.675 ^a				
<i>Reversed Wide Flow vs. Stationary Control</i>								
Foveal V1 (17)	-8,-98,8	5.61	5554	0.000	10,-98,4	6.25	sc	sc
Dorsal V2 (18)	-24,-104,10	6.13	sc	sc	22,-98,10	5.60	sc	sc
V5 (19/37)	-46,-78,2	5.31	sc	sc	50,-74,2	4.73	sc	sc
<i>Forward Wide Flow vs. Reversed Wide Flow</i>								
Ventral V5 (19/37)	-40,-74,-6	4.05	247	0.006	44,-70,-6	3.79	58	0.536 ^a
Lateral occipital (19)					44,-80,6	3.43	sc	sc ^a
Ventral occipito-temporal (37)					40,-56,-14	3.94	396	0.000
Fusiform gyrus (20)					46,-48,-16	4.18	sc	sc

Coordinates refer to the voxels of maximum activation within clusters of significant activation ($P < 0.05$, whole brain corrected at cluster-level), extent in voxelnumber and corrected P-values are additionally listed. Exceptions are the clusters marked with 'a' that reached significance at cluster-level ($P < 0.05$), but did reach significance after correction for the entire brain volume. Initial voxel-height threshold was $P < 0.001$, with extent threshold $k=8$ voxels. Positive x, y, z coordinates (in mm) indicate locations respectively right, anterior and superior to the middle of the anterior commissure. BA = Brodmann's area; IPS = Intraparietal Sulcus; sc = Same cluster, local maximum of activation is more than 8 mm apart from the adjoining focus in this cluster.

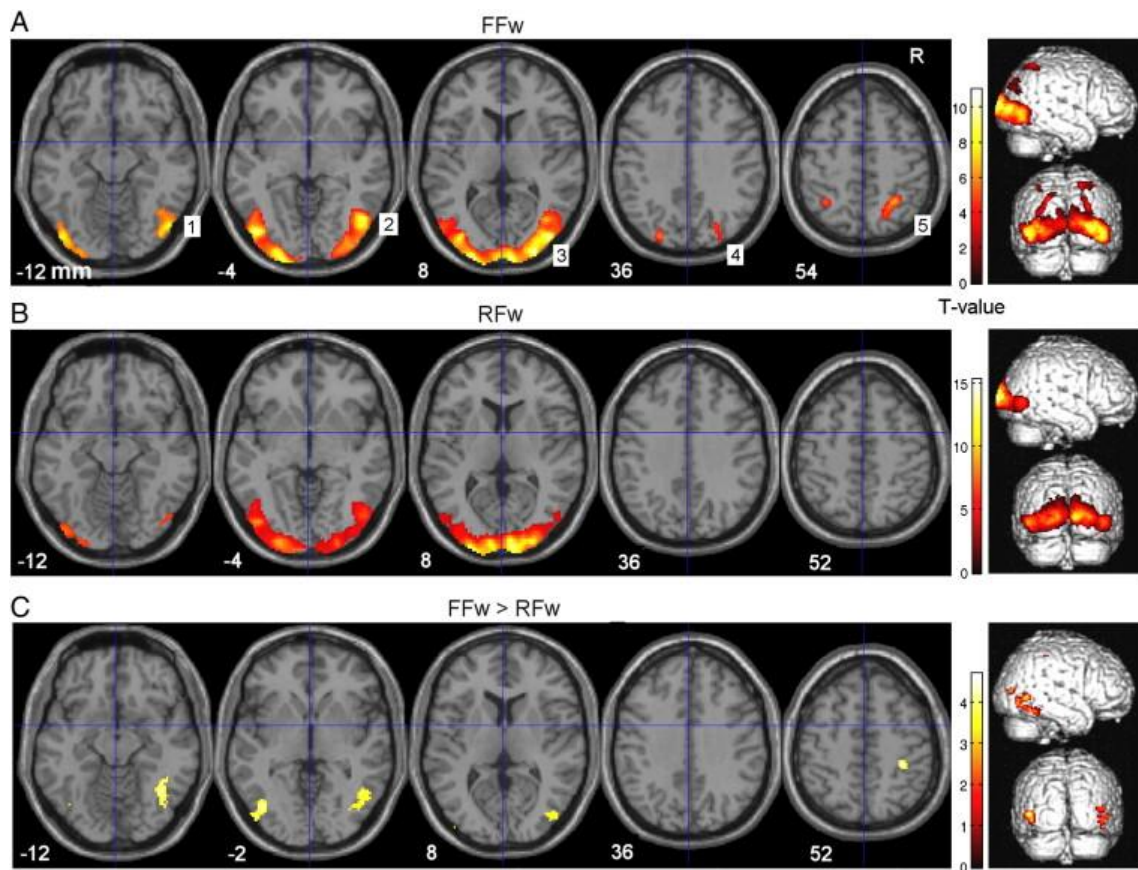
Table 2. Cerebral Activations related to Interruption of Wide Forward Flow.

Brain Region (BA)	Left				Right			
	x, y, z	Z-score	Extent	Pcorr.	x, y, z	Z-score	Extent	Pcorr.
<i>Transition Forward Wide to Narrow Flow vs. Stationary Control</i>								
Ventral V5 (19/37)	-46,-78,-10	4.08	138	0.005	46,-70,-8	3.69	315	0.000
Lateral occipital (19)					46,-86,-8	5.74	sc	sc
Putative area V2 (18)	-32,-96,-6	3.83	66	0.266 ^a	32,-100,-4	3.73	sc	sc
<i>Transition Forward Flow vs. Forward Wide Flow</i>								
Ventricle (temporal horn)	-22,-50,10	4.74	163	0.038				
Lateral occipital (19)					44,-90,-10	4.66	80	0.312 ^a
Medial prefrontal (8)	-8,34,46	3.38	13	0.994 ^b				
<i>Conjunction</i>								
<i>[Reversed Wide vs. Forward Wide Flow] + [Transition Forward vs. Forward Wide Flow]</i>								
Inferior prefrontal (11)	-26,50,4	4.61	344	1.000 ^b				
Medial prefrontal (8)	-6,34,46	3.88	684	0.962 ^a	12,30,44	3.33	sc	sc ^a

Coordinates refer to the voxels of maximum activation within clusters of significant activation ($P < 0.05$, whole brain corrected at cluster-level), extent in voxelnumber and corrected P-values are additionally listed. Exceptions are the clusters indicated with 'a' and 'b', indicating respectively $P < 0.05$ (cluster-level, uncorrected) and non-significant at cluster level. All clusters are generated with voxelheight threshold $P < 0.001$; extent threshold $k = 8$ voxels. Positive x, y, z coordinates (in mm) indicate locations respectively right, anterior and superior to the middle

of the anterior commissure. BA = Brodmann's area; sc = Same cluster, local maximum of activation is more than 8 mm apart from the adjoining focus in this cluster.

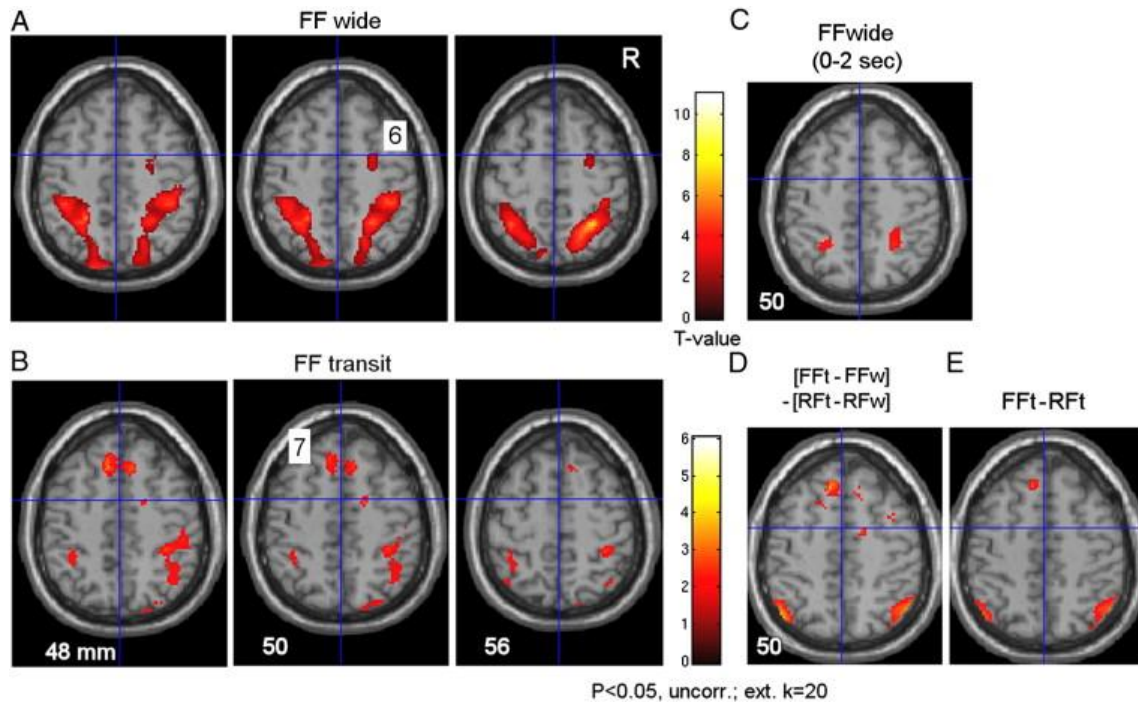
Figure 1. Cerebral activations evoked by wide-field optic flow.



Increases in Activation (SPM<math>T>; group of 15 subjects) related to wide-field forward flow (FFW) (A) and wide-field reversed flow (RFw) (B), each compared to the stationary control condition ($P<0.05$, corrected for the entire brain volume). The lower row (C) shows the increases of activation related to FFW contrasted to RFw ($P<0.001$, voxel-level uncorrected; extent $k=20$). Increased activations are projected on transverse anatomical sections of a standard brain volume (Montreal Neurological Institute, SPM 2005). At the right end of each row of transverse sections, the same activation clusters are rendered onto the surface of a standard anatomical brain volume (right-lateral and posterior views). Co-ordinates of the significant clusters are reported in Table 1. The hair-cross in the transverse sections indicates the cerebral midline and the VCA. The distance to the plane traversing the anterior- and posterior commissures (ac-pc) is indicated by the z co-ordinate (in mm, white numbers).

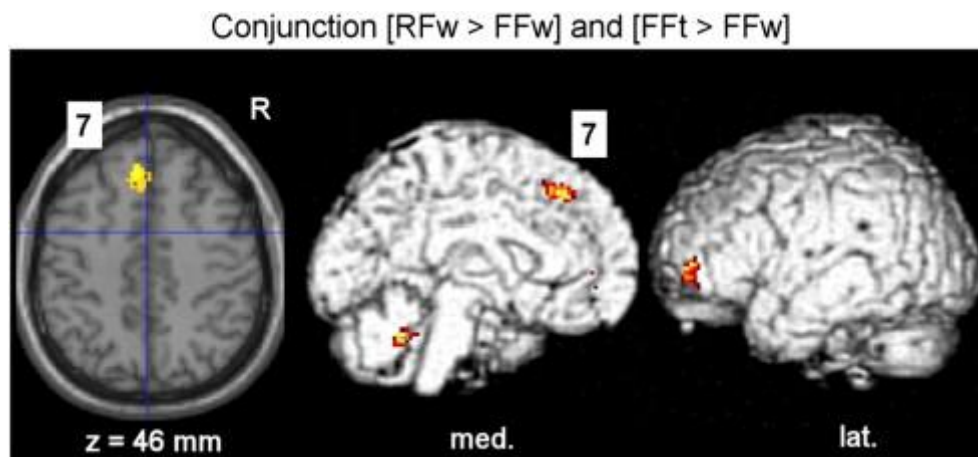
R= right side of the brain, 1= fusiform gyrus, 2= (ventral) V5, 3= lateral occipital region, 4= posterior intraparietal sulcus (pIPS), 5= superior parietal cortex.

Figure 2. Responses in visuomotor circuitry by interrupted optic flow.



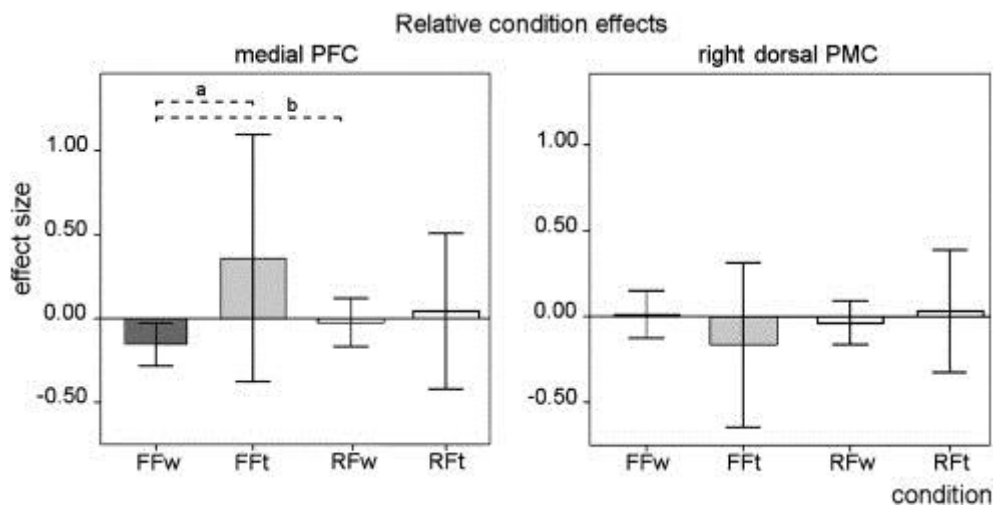
Increases in Activation related to wide-field forward flow (FFW, duration ranging from 6-12s) (A) and the transition to the narrow field of forward flow (FFt) (B), each compared to stationary control, particularly illustrating the activations in the dorsal premotor cortex PMd (6) and medial prefrontal cortex (7). Absence of medial prefrontal activation in the initial 2s frame of FFW following stationary control (C) and its presence after contrasting [FFt-FFw] to [RFt-RFw] (D) as well as FFt-RFt (E) provided arguments against confounding effects (see text) and supported the specificity of the relation between this medial prefrontal activation and FFt, mimicking the natural circumstance of naturally interrupting FFW by approaching a narrow corridor. Threshold for statistical significance was $P < 0.05$ (voxel-level uncorrected; extent $k=20$). Small volume correction for the right PMd activation (sphere; radius 10mm) resulted in a cluster-level corrected P-value of 0.275 (condition A), while for the medial prefrontal activation such P-value was 0.264 (B). For the contrasts D and E, performed to exclude confounds that might alternatively explain the medial prefrontal activation, corrected P-values were 0.220 and 0.345, respectively. Other conventions are similar to the description of Fig.1. Co-ordinates of FFt-related activations are reported in Table 2.

Figure 3. Medial prefrontal activation.



Increased activation in the medial prefrontal cortex (7) that resulted from conjunction analysis of the comparison FFt > FFw and the comparison of RFw > FFw (with inclusive masking) ($P < 0.001$, voxel-level uncorrected; extent $k=20$). The single focus of overlapping activations in the medial prefrontal cortex illustrates its selectivity. Other conventions are as in Fig.1. Next to the transversal section, medial and lateral views of a standard left hemisphere volume are depicted. Co-ordinates are reported in Table 2.

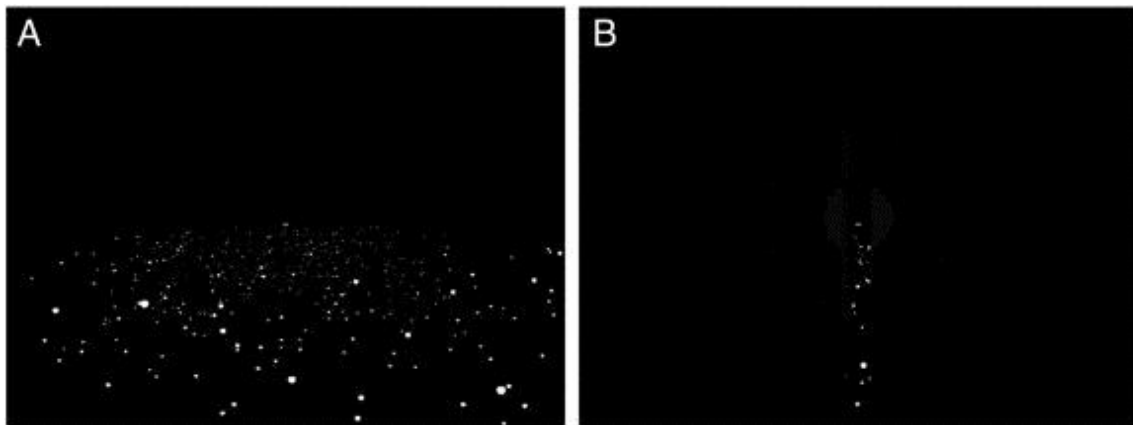
Figure 4. Relative condition effects in medial prefrontal- and dorsal premotor cortex.



Relative differences across the conditions Forward wide flow (FFw), Transition from forward wide to forward narrow flow (FFt), Reversed wide flow (RFw) and Transition from reversed wide to reversed narrow flow (FFt) are plotted for the clusters in the medial prefrontal cortex (max. x-8, y26, z48) and right dorsal premotor cortex (max. x28, y-6, z52). Regions of interest were defined by the demarcation of these clusters at $P < 0.05$; extent threshold 20 (see Fig.2.) The effect-size for each subject in these clusters was the mean voxel-value in each of the two clusters. It represents a percentage of the overall error term and is corrected to a mean of 0. The statistical significance of effect differences was assessed with ANOVA (medial PFC $P = 0.021$; dorsal PMC $P = 0.303$). Given the specific prediction of these differences, one-tailed P-values are presented for post-hoc tests. As to correct for multiple comparisons, threshold for statistical significance for the post-hoc tests was set at $P < 0.0125$.

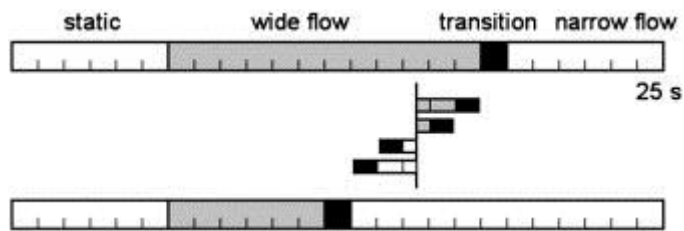
a: $P = 0.001$; b: $P = 0.168$.

Figure 5. Display of the stimulus presentation.



Distribution of dots displayed in the lower field of the monitor screen. The wide stimulus field is depicted on the left (A) and the narrow field on the right (B). The transition from wide to narrow fields was established by surfaces (in dark gray tone) that expanded in 1s from the horizon in both upward and downward direction. In 'forward flow', enlarging dots moved radial from the centre of the virtual horizon with increasing speed in the lower part of the screen. In 'reversed' flow, visual motion was in opposite direction during which the dots became smaller in size. Further details are explained in the methods section.

Figure 6. Arrangement of Conditions in Single Trials.



The visual stimulus conditions were presented in 6 blocks, each containing 12 trials. The upper and lower rows illustrate the fixed sequence of conditions in such trials, i.e. stationary control, wide field flow, transition and narrow flow. In each block, 6 trials had a radially expanding flow pattern ('forward flow') and 6 trials had contracting pattern ('reversed flow'), while in trials with the same flow-direction the transition from wide to narrow occurred respectively 6, 7, 8, 10, 11, or 12s after the onset of wide flow (illustrated by the 6 horizontal bars). The order of trials was randomized and balanced.